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|---|---|--|
| U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE<br>(REV. 11-2000)  |   | ATTORNEY'S DOCKET NUMBER<br>141-201                              |
| TRANSMITTAL LETTER TO THE UNITED STATES<br>DESIGNATED/ELECTED OFFICE (DO/EO/US)<br>CONCERNING A FILING UNDER 35 U.S.C. 371  |   | U S APPLICATION NO (If known, see 37 CFR 1.5<br><b>09/763831</b> |
| INTERNATIONAL APPLICATION NO.<br>PCT/US99/19847   | INTERNATIONAL FILING DATE<br>27 August 1999 | PRIORITY DATE CLAIMED<br>28 August 1998                          |
| TITLE OF INVENTION<br>OMEPRAZOLE FORMULATION  |   |  |
| APPLICANT(S) FOR DO/EO/US<br>CHIH-MING CHEN; JOSEPH CHOU & UNCHALEE KOSITPRAPA  |   |  |
| Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:   |   |  |
| <p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ul style="list-style-type: none"> <li>a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> has been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ul> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto.</li> <li>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</li> </ul> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> have been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ul> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> |   |  |
| <b>Items 11 to 20 below concern document(s) or information included:</b>  |   |  |
| <p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A <b>FIRST</b> preliminary amendment.</p> <p>14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input type="checkbox"/> Other items or information:</p>  |   |  |

|   |  |                                     |            |      |
|---|--|-------------------------------------|------------|------|
| U.S. APPLICATION NO. (if known) see 37 CFR 1.492(e)(5)<br><b>09/763831</b>  | INTERNATIONAL APPLICATION NO<br>PCT/EP99/06086 | ATTORNEY'S DOCKET NUMBER<br>141-201 |            |      |
| 21. <input checked="" type="checkbox"/> The following fees are submitted:<br><b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b><br>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1000.00<br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00<br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00<br>International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00<br>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00<br><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b> |  | <b>CALCULATIONS PTO USE ONLY</b>    |            |      |
|   |  | \$ 690.00                           |            |      |
| Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).  |  | \$ 130.00                           |            |      |
| CLAIMS  | NUMBER FILED                                   | NUMBER EXTRA                        | RATE       | \$   |
| Total claims  | 11 - 20 =                                      |                                     | x \$18.00  | \$ 0 |
| Independent claims  | 2 - 3 =  |                                     | x \$80.00  | \$ 0 |
| <b>MULTIPLE DEPENDENT CLAIM(S) (if applicable)</b>  |  |                                     | + \$270.00 | \$   |
| <b>TOTAL OF ABOVE CALCULATIONS =</b>  |  |                                     | \$ 690.00  |      |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.  |  |                                     | \$         |      |
|   |  | + \$                                |            |      |
| <b>SUBTOTAL =</b>   |  |                                     | \$ 820.00  |      |
| Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).  |  |                                     | \$         |      |
| <b>TOTAL NATIONAL FEE =</b>   |  |                                     | \$         |      |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +  |  |                                     | \$         |      |
| <b>TOTAL FEES ENCLOSED =</b>  |  |                                     | \$ 820.00  |      |
|   |  | <b>Amount to be refunded:</b>       | \$         |      |
|   |  | <b>charged:</b>                     | \$         |      |
| <p>a. <input checked="" type="checkbox"/> A check in the amount of \$ 820.00 to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.<br/>A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>08-1540</u>. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. <b>Credit card information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.</p>   |  |                                     |            |      |
| <p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</b></p>  |  |                                     |            |      |
| SEND ALL CORRESPONDENCE TO:<br>JAMES V. COSTIGAN, ESQ.<br>HEDMAN & COSTIGAN, P.C.<br>1185 AVENUE OF THE AMERICAS, SUITE 2003<br>NEW YORK, NY 10036-2646<br>212-302-8989   |  |                                     |            |      |
| <br><b>JAMES V. COSTIGAN</b><br>NAME _____<br>25,669<br>REGISTRATION NUMBER _____   |  |                                     |            |      |

OMEПRAZOLE FORMULATIONBACKGROUND OF THE INVENTION

The present invention relates to a stable formulation of omeprazole. It is well known that 5 omeprazole is sensitive to acidic conditions and after contact with an acid, omeprazole will degrade and will not function in its intended manner. Initially, alkaline materials were added to a core of omeprazole and later an enteric coating was applied over the core 10 to prevent the omeprazole from contacting the acidic pH conditions of the stomach. This approach is satisfactory if the product is administered within a short time after it is manufactured but if the product is stored under ambient conditions, the acidic residue 15 of the enteric coating appears to degrade the omeprazole before it is administered to a patient. To solve this problem, the prior art has used a separate layer of a coating agent to coat a pellet core which contains omeprazole and an alkaline material which is 20 thereafter coated with the enteric coating. This technique is described in U.S. 4,786,505. In addition WO 96/24338 discloses the use of an in situ formed interlayer that is based on the reaction of an aqueous enteric coating material with an alkaline material in 25 the core.

This dual layer coating technique requires the application of two separate functional coating operations which increases the length of the manufacturing process and the cost of the product. The 30 applicants have surprisingly discovered a coating system which avoids the need to use a coating layer to separate the omeprazole core from the enteric coating layer in an omeprazole dosage form. The separate coating system is based on the combined use of an 35 enteric coating agent which is applied to a pelletized core or a granular core of omeprazole as a suspension

in a suitable solvent.

The applicants have also surprisingly discovered that arginine or lysine can be used as a pH stabilizing agent.

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SUMMARY OF THE INVENTION

The present invention provides a novel stable pharmaceutical composition of omeprazole for oral administration which consists essentially of:

(a) a core of omeprazole or a pharmaceutically equivalent salt, a filler and an alkaline material selected from the group consisting of lysine and arginine; and

(b) a single layer of coating on said core which comprises a layer of an enteric coating agent applied from an organic based solvent coating system.

The core of the pharmaceutical composition can be in the form of a compressed tablet which is further comprised essentially of a surface active agent, and a binder. Alternatively, the pharmaceutical composition can have a pelleted core which is further comprised essentially of an inert core component, a surface active agent and a binder.

Accordingly, it is a primary object of this invention to provide a pharmaceutical dosage formulation of omeprazole which is stable upon prolonged storage, is stable when administered to a patient and is capable of providing the desired therapeutic effect.

It is also an object of this invention to provide a pharmaceutical dosage form of omeprazole which is bioequivalent to dosage forms of omeprazole which have an intermediate layer of an inert coating material.

It is also an object of this invention to provide

a stable dosage form of omeprazole which may be produced without the need to provide an intermediate coating layer that separates the omeprazole containing core from the enteric coating layer.

- 5        These and other objects of the invention will become apparent from a review of the appended specification.

DETAILED DESCRIPTION OF THE INVENTION

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The omeprazole formulation of the invention is preferably based on a core of omeprazole or pharmaceutically equivalent salt, a filler and an alkaline material selected from the group consisting of 15 arginine or lysine; and a single layer of coating on said core which comprises a layer of an enteric coating agent applied from an organic solvent based system. The Omeprazole core can either be pelleted or tabletted as described herein.

20       In the case of both the pelleted form and the tabletted form of the core a filler is used. A filler is used as a granulation substrate. Sugars such as lactose, dextrose, sucrose, maltose, or microcrystalline cellulose and the like may be used as 25 fillers in either the pellet or the granulation composition. In the case of the pelleted form the filler may comprise from 20 to 90wt% and preferably 65-85wt% based on the total weight of the drug layer composition. In the case of the tabletted form the 30 filler may comprise from 20 to 60wt% and preferably 20 to 40wt% based on the total weight of the granulation. In the case of the tabletted form of the invention a tablet disintegrant may be added which comprises corn starch, potato starch, croscarmelose sodium, 35 crospovidone and sodium starch glycolate in an effective amount. An effective amount which may be

from 3 to 10wt% based on the total weight of the granulation.

In the case of both the tabletted form and the pelleted form of the core an alkaline agent that is  
5 either lysine or arginine is used as a stabilizer. In the case of the tabletted form a level of from 20 to 60wt% and preferably 30 to 55wt% based on the weight of the granulation may be employed. In the case of the pelleted form a level of from 0.5 to 10wt% and  
10 preferably 1 to 3wt% based on the weight of the pellet may be employed.

In the case of both the pelleted form and the tabletted form of the invention an enteric coating agent is placed over the core. In both cases the  
15 enteric coating may comprise an acid resisting material which resists acid up to a pH of above about 5.0 or higher which is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate,  
20 carboxymethylethylcellulose, Eudragit L (poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit S (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B) and mixtures thereof.

The enteric coating agent may also include an inert processing aid in an amount in the case of the tabletted form from 15 to 55wt% and preferably 20 to 45wt% based on the total weight of the acid resisting component and the inert processing aid. In the case of  
25 the pelleted form the inert processing aid is preferably in an amount from 5 to 50wt% and most preferably 10-20wt%. The inert processing aids include finely divided forms of talc, silicon dioxide, magnesium stearate etc. Typical solvents which may be  
30 used to apply the acid resisting component-inert processing aid mixture include isopropyl alcohol,  
35

acetone, methylene chloride and the like. Generally the acid resistant component-inert processing aid mixture will be applied from a 5 to 20wt% of acid resisting component-inert processing aid mixture based on the 5 total weight of the solvent and the acid resistant component-inert processing aid.

- In the case of both the tabletted form and the pelleted form of the invention omeprazole or a pharmaceutically equivalent salt is used in the core.
- 10 In the tabletted formulation the omeprazole may comprise from 5 to 70wt% and preferably 10 to 30wt% of the granulation. In the pelleted form the Omeprazole may comprise from 10 to 50wt% and preferably 10 to 20wt% of the drug layer composition.
- 15 A surface active agent is used in both the tabletted and the pelleted form of the invention. The surface active agent may be any pharmaceutically acceptable, non-toxic surfactant. Suitable surface active agents include sodium lauryl sulfate, 20 polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 and the like. The surface active agent may be present at a level of from 0.1 to 5wt%. In the case of the tabletted form the surface active agent is preferably 0.20 to 2.0wt% based on the total weight of 25 the granulation. In the pelleted form the surface active agent is preferably 0.20 to 2.0wt% of the total weight of the drug layer composition.

- The binder is used in both the tabletted and the pelleted form of the invention. The binder may be any 30 pharmaceutically acceptable, non-toxic pharmaceutically acceptable binder. The binder is preferably a water soluble polymer of the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and 35 the like. A water soluble binder is preferred which is applied from an aqueous medium such as water at a level

of from 0.1 to 10wt% and preferably from 0.25 to 7.5wt% of binder based on the total weight of the granulation.

In the case of the tabletted form of the invention a granulation is formed by contacting the alkaline agent, the omeprazole, the surface active agent and the binder with a medium which may comprise any low viscosity solvent such as water, isopropyl alcohol, acetone, ethanol or the like. When fluids such as water are employed, this will usually require a weight of fluid which is about three times the weight of the dry components of the coating composition.

After the granulation is formed and dried, the granulation is tabletted and the tablets are directly coated with the enteric coating agent. A color imparting agent may be added to the enteric coating agent mixture or a rapidly dissolving seal coat containing color may be coated over the enteric coating agent layer provided that the seal coat is compatible with and does not affect the dissolution of the enteric coating layer. The rapidly dissolving seal coat may comprise Opadry pink which comprises approximately 91wt% hydroxypropyl methylcellulose (E-6), color and 9wt% polyethylene glycol which is applied as a 8-15%w/w solution in purified water. In addition the color may be provided as Chromateric which is available from Crompton & Knowles. This product contains water, talc, TiO<sub>2</sub>, triethyl citrate, propylene glycol, synthetic red iron oxide, potassium sorbate, xanthan gum, sodium citrate and synthetic yellow iron oxide. If desired, conventional sugar based seal coats may be used which contain FDA certified dyes.

In the case of a pelleted form the invention is preferably based on pellets having a core forming inert component which may comprise a starch or sugar sphere such as non-pareil sugar seeds having an average size of 14 to 35 mesh, preferably about 18 to 20 mesh. The

core forming inert component is coated with a formulation which comprises Omeprazole, a surface active agent, a filler, an alkaline material that is either lysine or arginine and a binder, which are 5 collectively referred to as the drug layer composition.

The core forming inert component is employed at 1:1 to 5:1 and preferably from 2:1 to 3:1 weight ratio to the drug layer composition.

The cores are formed by spraying the non-pareil 10 seeds with an aqueous or non-aqueous suspension which contains the alkaline agent, the omeprazole, the surface active agent and the binder. The suspension medium may comprise any low viscosity solvent such as water, isopropyl alcohol, acetone, ethanol or the like.

15 When fluids such as water are employed , this will usually require a weight of fluid which is about seven times the weight of the dry components of the coating composition.

After the cores are dried, the cores are coated 20 with the enteric coating agent. A color imparting agent may be added to the enteric coating agent mixture or a rapidly dissolving seal coat over the enteric coating agent layer provided that the seal coat is compatible with and does no affect the dissolution of 25 the enteric coating layer.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

Examples 1 to 5 describe a tabletted form of the 30 invention and Example 6 describes a pelleted form of the invention.

#### EXAMPLE 1

##### 35 Granulation.

A granulation containing omeprazole is formed in a fluid bed coater using a top spray granulation forming

suspension containing omeprazole, micronized to 95% less than 15 microns, 5%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose, 95%w/w of the total amount of L-arginine and sodium starch glycolate. The formulation for making the granulation has the following composition:

|    |  |         |
|----|--|---------|
| 10 | povidone, USP (Plasdone K90)             | 100.0g  |
|    | sodium starch glycolate                  | 100.0g  |
|    | sodium lauryl sulfate, NF/USP            | 6.0g    |
|    | microcrystalline cellulose (AvicelPH101) | 965.6g  |
|    | L-arginine, USP/FCC                      | 1020.0g |
| 15 | omeprazole, USP (micronized)             | 340.0g  |
|    | purified water, USP                      | 1100.0g |

#### **Tabletting.**

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with glyceryl monostearate:

|                                  |        |
|----------------------------------|--------|
| omeprazole granules              | 118.0g |
| glyceryl monostearate (Myvaplex) | 6.0g   |

Tabletting tools: 0.2812"  
 target weight : 124mg/tab  
 target hardness : 7Kp  
 LOD of granules : less than 3%

#### **Enteric coating.**

An enteric coating is applied to prepare enteric coated tablets as follows:

|    |  |        |
|----|--|--------|
| 35 | omeprazole tablets<br>(prepared above)     | 124.0g |
|    | hydroxypropyl methylcellulose<br>phthalate |        |

|    |   |        |
|----|---|--------|
|    |   | 14.7g  |
|    | talc  | 4.2g   |
| 5  | acetyl tributyl citrate   | 2.9g   |
|    | acetone   | 148.0g |
|    | isopropyl alcohol   | 148.0g |
| 10 | The solid coating materials were dissolved in the acetone and isopropyl alcohol and this solution was coated onto the omeprazole tablets using a perforated pan |        |

**Seal coat:**

15 A seal coat was applied to the enteric coated tablets as follows:

|    |   |        |
|----|---|--------|
|    | Enteric coated tablet   | 146.0g |
|    | Opadry II pink  | 4.5g   |
| 20 | Water   | 450.0g |
|    | The seal coat was applied onto the enteric coated omeprazole tablets using a perforated pan coater. |        |

25 EXAMPLE 2

**Granulation.**

A granulation containing omeprazole is formed in fluid bed coater using a top spray granulation forming 30 suspension containing omeprazole, micronized to 95% less than 15 microns, 2.68%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, polysorbate 80 and purified water which is sprayed onto a mixture of microcrystalline cellulose and 95.0%w/w of the total 35 amount of L-arginine. The formulation for making the granulation has the following composition:

|                              | mg/tablet |
|------------------------------|-----------|
| povidone, USP (Plasdone K90) | 5.88      |
| polysorbate 80 (Tween 80)    | 0.58      |

|   |       |
|---|-------|
| L-arginine, USP/FCC                       | 60.0  |
| omeprazole, USP (micronized)              | 20.0  |
| microcrystalline cellulose (Avicel PH102) | 25.54 |
| purified water, USP                       | n/a   |

5

**Tabletting.**

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with glyceryl monostearate:

|    |                                  |         |
|----|----------------------------------|---------|
| 10 | omeprazole granules              | 112.0mg |
|    | glyceryl monostearate (Myvaplex) | 6.8mg   |
|    | crospovidone XL                  | 16.2mg  |
|    | Tabletting tools: 0.2812"        |         |
|    | target weight : 135mg/tab        |         |
| 15 | target hardness : 7Kp            |         |
|    | LOD of granules : less than 3%   |         |

**Enteric coating.**

An enteric coating was applied to prepare enteric coated tablets as follows:

|    |  |         |
|----|--|---------|
| 25 | omeprazole tablets<br>(prepared above) | 135.0mg |
|    | Eudragit L30D-55                       | 14.0mg  |
|    | color (Chromateric)                    | 7.0mg   |
|    | 1M NaOH (to adjust pH to 5.0) qs       | na      |
| 30 | Purified water qs                      | na      |

The solid coating materials were dispersed in the water and this mixture was coated onto the omeprazole tablets using a perforated pan.

35

**EXAMPLE 3****Granulation.**

A granulation containing omeprazole is formed in

fluid bed coater using a top spray granulation forming suspension containing omeprazole, micronized to 95% less than 15 microns, 5.0%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose and 95.0%w/w of the total amount of L-arginine. The formulation for making the granulation has the following composition:

|   | mg/tablet |
|---|-----------|
| 10 povidone, USP (Plasdome K90)           | 5.0       |
| sodium lauryl sulfate                     | 0.3       |
| L-arginine, USP/FCC                       | 60.0      |
| omeprazole, USP (micronized)              | 10.0g     |
| microcrystalline cellulose (Avicel PH102) | 24.7      |
| 15 purified water, USP                    | n/a       |

#### Tabletting.

The granulation is tabletted into tablets containing 10mg of omeprazole by first mixing the 20 omeprazole granules with glyceryl monostearate:

|                                  |         |
|----------------------------------|---------|
| omeprazole granules              | 100.0mg |
| glyceryl monostearate (Myvaplex) | 5.0mg   |
| sodium starch glycolate          | 5.0mg   |
| Tabletting tools: 0.2812"        |         |
| 25 target weight : 110mg/tab     |         |
| target hardness : 7Kp            |         |
| LOD of granules : less than 3%   |         |

#### Enteric coating.

30 The tablets were coated with the same enteric coating that was applied to the tablets in Example 2.

#### EXAMPLE 4

##### 35 Granulation.

A granulation containing omeprazole is formed in

fluid bed coater using a top spray granulation forming suspension containing omeprazole, micronized to 95% less than 15 microns, 5.0%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose and 95.0%w/w of the total amount of L-arginine. The formulation for making the granulation has the following composition:

|                                 | mg/tablet |
|---------------------------------|-----------|
| 10 povidone, USP (Plasdone K90) | 5.88      |
| polysorbate 80                  | 0.60      |
| L-arginine, USP/FCC             | 60.0      |
| omeprazole, USP (micronized)    | 20.0      |
| crospovidone XL                 | 5.88      |
| 15 microcrystalline cellulose   | 25.54     |
| purified water, USP             | n/a       |

#### Tabletting.

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with glyceryl monostearate:

|                                  |         |
|----------------------------------|---------|
| omeprazole granules              | 117.9mg |
| glyceryl monostearate (Myvaplex) | 6.1mg   |
| Tabletting tools: 0.2812"        |         |
| 25 target weight : 124mg/tab     |         |
| target hardness : 7Kp            |         |
| LOD of granules : less than 3%   |         |

#### Enteric coating.

30 The tablets were coated with the same enteric coating that was applied to the tablets in Example 1.

#### EXAMPLE 5

35 The granulation of Example 1 was prepared and tabletted into tablets containing 20.0mg of omeprazole.

These tablets were coated as follows:

**Enteric coating.**

An enteric coating was applied to prepare enteric coated tablets as follows:

|    |  |          |
|----|--|----------|
| 5  | omeprazole tablets<br>(prepared above) | 126.00mg |
| 10 | Eudragit L30D-55                       | 17.00mg  |
|    | 1M NaOH (to adjust pH to 5.0) qs       | na       |
|    | acetyl tributyl citrate                | 1.70mg   |
| 15 | talc                                   | 3.80mg   |
|    | polysorbate 80                         | 1.50mg   |
| 20 | Purified water qs                      | na       |

The solid coating materials were dispersed in the water and this mixture was coated onto the omeprazole tablets using a perforated pan. A seal coat was applied using the procedure of Example 1.

**EXAMPLE 6**

In the case of a pharmaceutical formulation with a pelleted omeprazole core, the core is comprised of omeprazole, a surface active agent, a filler, an alkaline material and a binder.

Omeprazole activated pellets (sodium free) are prepared as follows: 13.650 kg of Purified water is dispensed into a suitably sized stainless steel container. L-Arginine Base (0.210 kg), Lactose Anhydrous, NF (1.75 kg) and Povidone (Plasdene <sup>®</sup>K-90) (0.056 kg) is added to the purified water while homogenizing at full speed (about 5,000 rpm). Homogenizing is continued until the materials are completely dissolved. Polysorbate 80, NF (0.044 kg) is added to the solution while homogenizing at a lower speed (700 -3300 rpm) to avoid excess foaming.

The material is homogenized until dissolved completely. Half of the solution (7.855 kg) is transferred into a 5-10 gallon stainless steel container. The original container is hereafter referred to as "container A" and the new container is henceforth referred to as "container B." Micronized omeprazole 95% less than 15 microns (0.980 kg) is added to container A while homogenizing at a lower speed (700-3300 rpm) to avoid excess foaming. The Omeprazole is allowed to disperse into the solution completely and then homogenized for another 10 minutes. The homogenizer is replaced with a mechanical stirrer and the suspension is continuously stirred throughout the coating process. When approximately three fourth of the omeprazole suspension in container A is consumed, 0.980 kg of micronized omeprazole is added to container B while homogenizing at a lower speed (700-3300) to avoid excess foaming. The Omeprazole is allowed to disperse in the solution completely and homogenization is continued for another 10 minutes. The homogenizer is replaced with a mechanical stirrer and the suspension is continuously stirred throughout the coating process. 9.98 kg of sugar spheres are added to a fluidized bed coater and preheated until the product reaches 40-45°C. The drug suspension from containers A and B are sprayed onto the spheres. The atomization pressure is between 1.5 to 3.5 bar and the pump rate is 2-100 ml/min. The spray rate does not exceed 20ml/min in the first two hours to avoid agglomeration of the sugar spheres. The coating suspension is transferred to a smaller container to facilitate stirring when the surface of the coating suspension reaches the stirring blade. After the coating suspension has been consumed the pump is stopped and the fluidization is continued in the fluidized bed coater with the heat off until the

product temperature drops below 32°C.

The pellets are then transferred to a fluidized bed coater into a 50°C oven (45-55°C). The pellets are dried until the moisture content of the pellets is not more than 2.5%. The pellets are separated into different size fractions by using a SWECO Separator equipped with 14 and 24 mesh screens. The pellets are collected in doubled polyethylene lined plastic containers and stored with desiccant.

10 ENTERIC COATING PROCESS

10.844 kg of isopropyl alcohol, USP is dispensed into a suitably sized stainless steel container. 10.844 kg of acetone is added to the isopropyl alcohol. 1.683 kg of hydroxypropyl methylcellulose phthalate (Hypromellose 55, Substitution type 200731) and cetyl alcohol, NF (0.084 kg) are added to the solution while homogenizing at full speed until all the materials are dissolved completely. The homogenizer is then removed and replaced with a mechanical stirrer.

Talc (1.683 kg) is added while stirring. The talc is mixed until fully dispersed in the solution and the mixing is continued throughout the entire coating process. A fluidized bed coater is preheated to 32°C. The omeprazole active pellets (11.550 kg) are loaded into the fluidized bed coater and preheated until the temperature reaches 30°C.

The coating suspension is sprayed on the pellets using a product temperature of 25-35°C, an atomization pressure of 1.5 to 3.0 bar and a pump rate of 200-300 ml/min. The coating suspension is transferred to a smaller container to facilitate stirring when the surface of the coating suspension reaches the stirring blade.

35 After the coating suspension has been consumed the coated pellets are dried in a fluidized bed

coater for 20 minutes using the same coating conditions except lowering the atomization pressure to 2 bars or below. The coated pellets are discharged into double polyethylene bags. The 5 pellets are separated into different size fractions by using a SWECO separator equipped with 14 and 24 mesh screens. The pellets which are larger than 14 mesh and smaller than 24 mesh are rejected. The pellets that passed through the 14 mesh and retained 10 on the 24 mesh are retained in polyethylene bags.

#### BLENDING

Omeprazole enteric coated pellets (Sodium Free), blended are prepared as follows:

14.400 kg of omeprazole enteric coated pellets 15 (Sodium free) are charged into a blender. Talc, USP (0.225 kg) is sprinkled on top of the pellet bed and then blended at 28 rpm for 5 minutes. 0.2 to 0.5 grams of each sample is withdrawn into separate vials from the blender. The blended pellets are unloaded 20 into plastic containers lined with double polyethylene. The excess talc is screened off using a SWECO separator equipped with a 24 mesh screen. The pellets are collected in containers lined with double polyethylene bags and stored with desiccant.

#### ENCAPSULATION

An encapsulation room is prepared in which the relative humidity is in the range of 35-65% and the temperature is in the range of 15-25°C. Omeprazole enteric coated pellets (Sodium Free) blended are 30 encapsulated using the following equipment and guidelines. A capsule machine model MACOFAR MT-20 is prepared for the procedure placing the machine setting at 4, using capsule machine size part 1, capsule magazine 1. The target filled capsule weight 35 is 457.15 mg. If the total weight is not within 3% of the target weight, further adjustment must be

performed. Capsule fill verification is performed at twenty minutes intervals on ten individual capsules.

Acceptable capsules are collected in containers lined with double polyethylene bags and placed under  
5 desiccant.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are  
10 skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

15

## Claims:

1. A stable pharmaceutical composition of omeprazole for oral administration which consists essentially of:
  - 5 (a) a core of Omeprazole or a pharmaceutically equivalent salt, a filler and an alkaline material selected from the group consisting of lysine and arginine; and
  - (b) a single layer of coating on said core which
- 10 comprises a layer of an enteric coating agent applied from an organic solvent based system.
2. A pharmaceutical composition of omeprazole as defined in claim 1 wherein said core is further comprised essentially of a surface active agent, and a binder and said pharmaceutical composition is formed into a compressed tablet.
- 15 3. A pharmaceutical composition as defined in claim 1 wherein said core is further comprised essentially of a an inert core component, a surface active agent and a binder and said pharmaceutical composition is pelleted.
- 20 4. A pharmaceutical composition of omeprazole as defined in claim 2 wherein the acid resistant component is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters.
- 25 5. A pharmaceutical composition of omeprazole as defined in claim 3 wherein the acid resistant component is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate,

carboxymethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters.

6. A pharmaceutical composition of omeprazole as  
5 defined in claim 1 wherein the enteric coating agent  
also includes an inert processing aid.

7. A pharmaceutical composition of omeprazole as  
defined in claim 1 wherein the enteric coating agent  
10 around the core includes from 5 to 55wt% by weight of  
the coating of an inert processing aid.

8. A pharmaceutical composition of omeprazole as  
defined in claim 1 which includes a sodium lauryl  
15 sulfate as the surface active agent.

9. A pharmaceutical dosage formulation which consists  
essentially of:  
20 (a) a tablet core comprising omeprazole, a binder, an  
alkaline agent selected from the group consisting of  
arginine or lysine, a filler; and  
(b) an enteric coating agent around said core, said  
enteric coating comprising hydroxypropylmethyl  
cellulose phthalate and talc.  
25

10. A pharmaceutical composition as defined in claim 3  
wherein the core contains a non-pariel sugar seed.

11. A pelleted pharmaceutical dosage formulation which  
30 consists essentially of:  
(a) a core comprising a non-pariel sugar seed coated  
with drug layer composition comprising omeprazole,  
a binder, an alkaline agent selected from the list  
consisting of arginine and lysine, a filler and a  
35 surface active agent; and  
(b) an enteric coating agent around said core, said

enteric coating comprising hydroxypropylmethyl cellulose phthalate and talc which is applied from an organic solvent based system.

Docket No: 141-201

**APPLICATION FOR UNITED STATES LETTERS PATENT  
DECLARATION, POWER OF ATTORNEY, AND PETITION**

As a below-named inventor, I declare that:

My residence, post office address and citizenship are as stated next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the invention which is described and which is claimed in the specification, entitled: OMEPRAZOLE FORMULATION

The specification [ ] is attached hereto  was filed on February 26, 2001, as Application Serial No. 09/763,831.

I hereby state that I have reviewed and understand the contents of said specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.<sup>1</sup>

| COUNTRY | APPLICATION NUMBER | DATE<br>(Day, Month, Year) | PRIORITY CLAIMED<br>UNDER 35 U.S.C. 119 |
|---------|--------------------|----------------------------|---|
|         |                    |                            | Yes [ ] No [ ]                          |
|         |                    |                            | Yes [ ] No [ ]                          |

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

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<sup>1</sup>In Non-Convention cases, a listing of all filings and current status of cases filed more than a year before the U.S. filing is required to comply with 37 CFR 1.56(a). Such a listing may be attached.

| APPLICATION SERIAL NO. | FILING DATE    | STATUS |
|------------------------|----------------|--------|
| PCT/US99/19847         | 27 August 1999 |        |
|                        |                |        |

I hereby appoint my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith:

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The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| INVENTOR(S)   | DATE  | RESIDENCE AND<br>P.O. ADDRESS                                     |
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